CLAIMS

1. A method for identifying an agent that increases Foxa-2 expression comprising contacting a plurality of cells that contain a Foxa-2 promoter operably linked to a coding sequence for Foxa-2 or a reporter gene with a candidate agent; assaying for expression of Foxa-2 or the reporter in the presence and absence of the candidate agent; and comparing Foxa-2 or reporter expression in the presence and absence of the candidate agent, whereby an increase in Foxa-2 or reporter expression in the presence of the candidate agent is indicative of the identification of an agent that increases Foxa-2 expression.

2. The method of Claim 1 wherein the cells are mammalian cells.

3. The method of Claim 2 wherein the cells are human cells.

4. The method of Claim 3 wherein the cells are human preadipocytes or adipocytes.

5, The method of Claim 1 wherein the cells are 3T3-L1 cells.

6. The method of Claim 1 wherein the cell contains a construct comprising a Foxa-2 promoter operably linked to a coding sequence for Foxa-2.

7. The method of Claim 6 wherein the coding sequence encodes an adipocyte-specific Foxa-2 isoform.

8. The method of Claim 1 wherein Foxa-2 expression is assayed by detecting Foxa-2 mRNA.

9. The method of Claim 8 wherein Foxa-2 mRNA is detected by Northern blotting or polymerase chain reaction.

10. The method of Claim 1 wherein Foxa-2 expression is assayed by detecting Foxa-2 protein.

11. The method of Claim 10 wherein Foxa-2 protein is detected by Western blotting or immunohistochemistry.

12. The method of Claim 1 wherein the reporter gene is selected from the group consisting of the chloramphenicol acetyl transferase gene, the beta-galactosidase gene, the beta-glucuronidase gene, the green fluorescence protein gene and the luciferase gene.

13. The method of Claim 1 wherein the cell is 3T3-L1 cell stably transformed with a construct comprising a Foxa-2 promoter operably linked to the coding sequence of the luciferase gene.

14. A composition comprising an agent identified by the method of Claim 1.

15. A method for identifying an agent that increases Fxr expression comprising contacting a plurality of cells that contain a Fxr promoter operably linked to a coding sequence for Fxr or a reporter gene with a candidate agent; assaying for expression of Fxr or the reporter in the presence and absence of the candidate agent; and comparing Fxr or reporter expression in the presence and absence of the candidate agent, whereby an increase in Fxr or reporter expression in the presence of the candidate agent is indicative of the identification of an agent that increases Fxr expression.

16. The method of Claim 15 wherein the cells are mammalian cells.

17. The method of Claim 16 wherein the cells are human cells.

18. The method of Claim 17 wherein the cells are human preadipocytes or adipocytes.

19. The method of Claim 15 wherein the cells are 3T3-L1 cells.

20. The method of Claim 15 wherein the cell contains a construct comprising a Fxr promoter operably linked to a coding sequence for Fxr.

21. The method of Claim 20 wherein the coding sequence encodes human Fxr.

22. The method of Claim 15 wherein Fxr expression is assayed by detecting Fxr mRNA.

23. The method of Claim 22 wherein Fxr mRNA is detected by Northern blotting or polymerase chain reaction.

24. The method of Claim 15 wherein Fxr expression is assayed by detecting Fxr protein.

25. The method of Claim 24 wherein Fxr protein is detected by Western blotting or immunohistochemistry.

26. The method of Claim 15 wherein the reporter gene is selected from the group consisting of the chloramphenicol acetyl transferase gene, the beta-galactosidase gene, the beta-glucuronidase gene, the green fluorescence protein gene and the luciferase gene.

27. The method of Claim 15 wherein the cell is 3T3-L1 cell stably transformed with a construct comprising a Fxr promoter operably linked to the coding sequence of the luciferase gene.

28. A composition comprising an agent identified by the method of Claim 15.

29. A method of identifying an agent that activates Fxr comprising contacting a plurality of cells that contain Fxr with a candidate agent; assaying for activation of Fxr in the presence and absence of the candidate agent; and comparing activation of Fxr in the presence and absence of the candidate agent, wherein an increase in activation in the presence of the agent is indicative of the identification of an agent that activates Fxr.

30. The method of Claim 29 wherein the cells contain a vector comprising an Fxr promoter operably linked to a reporter gene, and activation of Fxr is assayed by measuring reporter gene activity.

31. The method of Claim 29 wherein Fxr activation is assayed by measuring increased expression of Fxr target genes.

32. A composition comprising an agent identified by the method of Claim 29.

33. A method of inhibiting adipogenesis comprising contacting a cell with an agent identified by the method of any one of Claims 2, 15 and 29.

34. A method for treating obesity, metabolic syndrome or Type 2 diabetes comprising administering to a subject in need of such treatment a composition comprising an agent identified by the method of any one of Claims 1, 15 and 29.

35. A method for inhibiting adipogenesis comprising contacting a cell capable of adipogenesis with an agent selected from the group consisting of an agent that increases levels of Foxa-2 mRNA, an agent that increases levels of Foxa-2 protein, an agent that increases levels of Fxr mRNA, an agent that increases levels of Fxr protein, and an agent that activates Fxr.

36. The method of Claim 35 wherein the agent that increases levels of Foxa-2 protein is Foxa-2 protein or a vector that expresses Foxa-2 protein.

37. The method of Claim 35 wherein the agent that increases levels of Fxr protein is Fxr protein or a vector that expresses Fxr protein.

38. A method for treating obesity, metabolic syndrome or Type 2 diabetes comprising administering to a subject in need of such treatment a composition comprising an agent selected from the group consisting of an agent that increases levels of Foxa-2 mRNA, an agent that increases levels of Foxa-2 protein, an agent that increases levels of Fxr mRNA, an agent that increases levels of Fxr protein, and an agent that activates Fxr.

39. A method of identifying an agent that inhibits the phosphorylation of Foxa-2 comprising combining a candidate agent with a polypeptide having Akt kinase activity and a substrate comprising the phosphorylation domain of Foxa-2; assaying for phosphorylation of the substrate in the presence and absence of the candidate agent; and comparing phosphorylation in the presence and absence of the candidate agent, whereby a decrease in phosphorylation of the substrate in the presence of the candidate agent is indicative of the identification of an agent that inhibits phosphorylation of Foxa-2.

40. The method of Claim 39 wherein the polypeptide having Akt kinase activity is human Akt 1 or human Akt 2.

41. The method of Claim 39 wherein the substrate is a Foxa-2 protein or fragment thereof comprising the phosphorylation domain.

42. The method of Claim 39 wherein the substrate is human Foxa-2.

43. A composition comprising an agent identified by the method of Claim 39.

44. A method of identifying an agent that inhibits the nuclear exclusion of Foxa-2 in hepatocytes comprising contacting a plurality of hepatocytes, under conditions whereby Foxa-2 exhibits nuclear exclusion, with a candidate agent; determining the intracellular location of Foxa-2 in the presence and absence of the candidate agent; and comparing the intracellular location of Foxa-2 in the presence and absence of the agent, whereby an increase in nuclear localization of Foxa-2 in the presence of the candidate agent is indicative of the identification of an agent that inhibits nuclear exclusion of Foxa-2 in hepatocytes.

45. The method of Claim 44 wherein the hepatocytes are HepG2 cells.

46. The method of Claim 44 wherein the hepatocytes are contained within the liver of a mammal.

47. The method of Claim 44 wherein intracellular location of Foxa-2 is determined by Western blotting, immunohistochemistry, or measurement of expression of Foxa-2-activated genes.

48. A composition comprising an agent identified by the method of Claim 44.

49. A method of treating obesity, type 2 diabetes or hyperinsulinemia comprising administering to a subject in need of such treatment the composition of Claim 39.

50. A method of treating obesity, type 2 diabetes or hyperinsulinemia comprising administering to a patient in need of such treatment the composition of Claim 48.